COST ESTIMATE FOR THE PRODUCTION OF
HEAT TREATED FACTOR VIII CONCENTRATE

Protein Fractionation Centre
21 Ellen's Glen Road
EDINBURGH

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1. **INTRODUCTION**

Considerable progress has been made at PFC in developing methods and technologies designed to provide non-infective factor VIII concentrate at a yield sufficient to maintain SNS commitments.

Two small lots of heat treated FVIII were issued for clinical evaluation during 1983. This material was prepared using a heating method similar in its viral inactivation capacity to the best of the various heating processes known to be used by other manufacturers. Although the clinical results were encouraging, viral studies carried out at PFC during 1983 indicated that the method was inferior to that used to inactivate virus in albumin solutions. A more severe heating method has therefore been developed at PFC and a small amount of product should soon be available for preliminary clinical evaluation.

Subject to proper funding being available for this development the timescale for the introduction of this new product is expected to be:-

- **April 1984**: Advanced heat treated product available for clinical evaluation.
- **January 1985**: Commissioning of full-scale production using specially designed equipment and facilities.
- **April 1985**: All FVIII produced by new method and available for clinical use.

The timetable assumes that clinical evaluation of the product is satisfactory and that building modifications within PFC can be incorporated into the phase IIa building programme scheduled for October 1984.

2. **PROCESS METHODS**

2.1 **Introduction**

Although heat treatment is the essential component of the process there are a number of other difficult features which result from the use of a sugar stabiliser (used to stabilise FVIII during pasteurisation) and the need to prevent re-contamination with virus following heat treatment (eg from working in close proximity to other plasma products). The cost implications of these features are estimated in section (3) below however it is important to appreciate that these are necessary and vital to the routine attainment of a high quality product and to GMP in the wider sense.

2.2 **Solids Handling**

The full-scale process is being designed to handle plasma in 1000 kg lots. At this scale each lot will utilise about 120 kg sorbitol as the major stabilising additive; the sorbitol must be used in powder form (somewhat like icing sugar) and strict control and containment of this material will be essential to prevent contamination of PFC with a sticky surface film.

Specialist equipment is available but this, and the facilities for reagent storage, will have to be very carefully defined to ensure that the powder is appropriately contained at all times.
2.3 Prevention of Re-contamination with Virus

All of the plasma fractions are potentially contaminated with virus during processing (including albumin which is only pasteurised in the final container). Where fractions are processed in common areas, perhaps using common equipment, then there is a clear risk of cross-contamination from one fraction to another. While this risk can be minimised by careful cleaning, sterilisation and discipline this may not be sufficiently secure to guarantee continued non-infectivity of a fraction pasteurised in-process (rather than in the final container).

For adequate security, further processing of the pasteurised FVIII should be carried out in a specially designed, dedicated area using dedicated equipment (see figure). Although such an area would initially be used for FVIII production, other products pasteurised in-process could also utilise this area as these developments come to fruition (e.g. FIX, ATIII, fibronectin).

2.4 Recovery Process

A particularly difficult feature of this process is the need to recover FVIII which has been diluted in large volumes of concentrated sugar. Two alternative techniques have been developed and evaluated for this purpose:

(i) Ultrafiltration & Diafiltration

Pilot-scale studies on this technique have been completed and the two lots of FVIII issued for clinical evaluation in 1983 were processed using this method.

(ii) Precipitation & Centrifugation

Because of early difficulties with the ultrafiltration method studies of this alternative option have been carried out at laboratory scale. Results from this work have been very promising indicating that the technique is more robust for use in a routine production environment and that a higher quality concentrate can be produced, with a similar yield to the ultrafiltration method. This is therefore the method of choice at the moment and the cost estimates below have been calculated on this basis. However the method has still to be evaluated at pilot-scale and, although unlikely, a change back to ultrafiltration may be required if performance is not maintained on scale-up.

If ultrafiltration is finally selected, the costs will be very similar to those of the precipitation method and separate costs have not therefore been given.

3. COST ESTIMATES

3.1 Capital

3.1.1 Equipment

<table>
<thead>
<tr>
<th>Equipment</th>
<th>Cost £</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pasteurisation system (1)</td>
<td>15 000</td>
</tr>
<tr>
<td>Process vessels (incl instrumentation) (5)</td>
<td>15 000</td>
</tr>
<tr>
<td>Agitators (4)</td>
<td>9 000</td>
</tr>
<tr>
<td>Pumps (4)</td>
<td>5 000</td>
</tr>
<tr>
<td>Centrifuges (2)</td>
<td>23 000</td>
</tr>
<tr>
<td>Solids handling system (1)</td>
<td>6 000</td>
</tr>
<tr>
<td>c/f</td>
<td>73 000</td>
</tr>
</tbody>
</table>


3.1.2 Environmental Control, etc

<table>
<thead>
<tr>
<th>Description</th>
<th>Cost (£)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Building modifications</td>
<td>9,000</td>
</tr>
<tr>
<td>Provision of services</td>
<td>3,000</td>
</tr>
<tr>
<td>Air control (sterile filtration)</td>
<td>5,000</td>
</tr>
</tbody>
</table>

Total Capital Cost = £90,000

3.2 Revenue (Additional)

<table>
<thead>
<tr>
<th>Description</th>
<th>Cost (£)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reagents</td>
<td>15,000</td>
</tr>
<tr>
<td>Materials (e.g., filtration)</td>
<td>3,000</td>
</tr>
<tr>
<td>Maintenance (10% of capital)</td>
<td>9,000</td>
</tr>
</tbody>
</table>

Total additional revenue cost = £27,000

3.3 Travel

It will be necessary to visit manufacturers to specify and inspect specialist equipment. Estimated cost of travel and subsistence = £700.

3.4 Staffing

This development will have staffing implications but these must be considered in the context of the overall staffing requirements of the Centre. This aspect has therefore not been included in this report.
FACTOR VIII PASTEURISATION PROCESS

FACTOR VIII SOLUTION

SORBITOL

PASTEURISATION SYSTEM

HOT WATER SUPPLY

DILUENT

DILUTION

FILTRATION

PRECIPITATION

SUPERNATANT TO DRAIN

FACTOR VIII SOLUTION TO STERILE FILTRATION

PRODUCT FORMULATION

CENTRIFUGE

WASH PRECIPITATE

CENTRIFUGATION